10/521974

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P100558WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/03089	International filing date *(day/month/year)* 18.07.2003	Priority date *(day/month/year)* 23.07.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/575		
Applicant BIOACTA LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the opinion
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.02.2004	11.11.2004
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Kronester-Frei, A Telephone No. +49 89 2399-8555

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/03089

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-22 as originally filed

Claims, Numbers

1-39 received on 05.06.2004 with letter of 03.06.2004

Drawings, Sheets

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 34-36

   because:

   ☒ the said international application, or the said claims Nos. 34-36 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-28,32,33
	No:	Claims	29-31,37-39
Inventive step (IS)	Yes:	Claims	1-28,32,33
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-28,32,33
	No:	Claims	34-36

2. Citations and explanations

see separate sheet

Re Item I

Basis of the opinion

Reference is made to the following documents:

D1: REUBI JEAN CLAUDE ET AL: "Y1-mediated effect of neuropeptide Y in cancer: Breast carcinomas as targets" CANCER RESEARCH, vol. 61, no. 11, 1 June 2001 (2001-06-01), pages 4636-4641, XP002262055 ISSN: 0008-5472

D2: WO 95 00161 A (UNIV CINCINNATI ;BALASUBRAMANIAM AMBIKAIPAKAN (US)) 5 January 1995 (1995-01-05)

D3: MICHEL MARTIN C ET AL: "XVI. International union of pharmacology recommendations for the nomenclature of neuropeptide Y, peptide YY, and pancreatic polypeptide receptors" PHARMACOLOGICAL REVIEWS, vol. 50, no. 1, March 1998 (1998-03), pages 143-150, XP002262056 ISSN: 0031-6997

D4: WAHLESTEDT C ET AL: "NEUROPEPTIDE Y-RELATED PEPTIDES AND THEIR RECEPTORS-ARE THE RECEPTORS POTENTIAL THERAPEUTIC DRUG TARGETS?" ANNUAL REVIEW OF PHARMACOLOGY AND TOXICOLOGY, ANNUAL REVIEW INC., PALO ALTO, CA, US, vol. 32, 1993, pages 309-352, XP000612055 ISSN: 0362-1642

D5: GEHLERT D R: "SUBTYPES OF RECEPTORS FOR NEUROPEPTIDE Y: IMPLICATIONS FOR THE TARGETING OF THERAPEUTICS" LIFE SCIENCES, PERGAMON PRESS, OXFORD, GB, vol. 55, no. 8, 1994, pages 551-562, XP000612039 ISSN: 0024-3205

D6: YU A ET AL: "Vitamin E and the Y4 agonist BA-129 decrease prostate cancer growth and production of vascular endothelial growth factor" JOURNAL OF SURGICAL RESEARCH, vol. 105, no. 1, 1 June 2002 (2002-06-01), pages 65-68, XP002262057 ISSN: 0022-4804

D7: BEHR T M ET AL: "IMPROVED PROSPECTS FOR CANCER THERAPY WITH RADIOLABELED ANTIBODY FRAGMENTS AND PEPTIDES?" JOURNAL OF NUCLEAR MEDICINE, SOCIETY OF NUCLEAR MEDICINE. NEW YORK, US, vol. 37, no. 5, May 1996 (1996-05), pages 834-836, XP000978767 ISSN: 0161-5505

D8: WO 02 051857 A (NANDABALAN KRISHNAN ;CHEW ANNE (US); DENTON R REX (US); GENAISSANC) 4 July 2002

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For the assessment of the present claim 34-36 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The Search has been carried out on the basis of the sequence listing indicated in

Figure 6/6. Since the sequences concerned are rather short it was possible to effect the search without the presence of an Sequence Listing being filed in a form which satisfies the requirements of the PCT (Rule 13ter.1 PCT).

D1: Neuropeptide Y is found to inhibit the growth of the Y1-expressing SK-M-MC cells in culture.
D2: Neuropeptide y Antagonists (NPY(18-36) und agonists (NPY (1-36). NPY (1-36) is a potent vasoconstrictor or orexigenic agent, peptides related to them can suppress or inhibit the deleterious effects of NPY. Antagonists are useful for controlling feeding disorders and blood pressure. Carboxy portion of cardiac receptor antagonist = NPY (18-36).
D3: Receptor oriented classification of Neuropeptide Y, Peptide YY
D4: Neuropeptide Y related peptides, identification and postulated therapeutic uses
D5: Receptor corresponding to neuropeptide Y and derivatives, Subtypes in Table 1 (NPY 13-36). NPY as a potent and long lasting vasoconstriction, this effect is not mimicked by the C-terminal fragments NPY 13-36 and PYY 13-36
D6: Gastrointestinal hormone peptide, similar to neuropeptide Y, has a growth inhibitory activity against multiple cancer cell lines and is synergistic with ATS (=RRR-alpha tocopheryl succinate) against breast and pancreatic cancer growth.
D7: Radioimaging of peptides
D8: Polynucleotides comprising one or more of 8 novel single nucleotide polymorphism in the human Neuropeptide Y (NPY) gene are described.

1. The use claims 1-15, 27 drafted in the format of second medical use claims have been restricted to the preparation of a medicament for use in the treatment of diseases or conditions which would benefit from inhibition of angiogenesis are considered to be novel.

As far as the requirements of inventive step of claims 1-15, 27 and purely dependent subject-matter is concerned it would appear that the person skilled in this art confronted with the problem of looking for peptides having cell-cycle inhibitory and anti-angiogenesis activity would have been able to deduce in an obvious manner form the teaching of D1 in combination with D2-D5 that the neuropeptide Y would be a suitable as peptide of origin to effect typical modifications/substitutions etc, since these pepdides are known to inhibit tumour cell growth. Although D1 does not explicitly say that the activity described therein is not related to the inhibition of tubule formation and inhibition of endothelial cells growth, it cannot be excluded that this is an inherent feature of the inhibition of the activity mentioned in D1, the tumour cell growth inhibition

in combination with vasoconstriction (D5). The argumentation available is not considered to be convincing in this context.
In particular it is not apparent why on one side the C-terminal substitution pattern Y==>T seems to reflect the focus of the invention and on the other side exactly this part is not excluded from variability (Article 5 PCT in context with Article 33(3) PCT).

2. Novelty of claims 16-26, 28, 32, 33 can also be acknowledged, because nowhere in the prior art agents comprising 2 or more peptides have been disclosed.

However, since these claims (first medical use type of claims) comprise subject-matter which is not limited to ARYYSALRHYINLITRQRT but could include also ARYYSALRHYINLITRQRY including modifications by addition, deletion or substitution of at least... nucleic acid which hybridizes..." including nucleic acid molecules corresponding to the

- the carboxy portion of Neuropeptide Y but also the carboxy portion of Peptide YY (D1), but also
- the neuropeptide Y and the Peptide YY themselves)

the requirements of inventive step are not present. In fact it appears to be obvious in this respect in order to develop a novel agent having the same spectrum of activity (anticancer activity) comprising the known ARYYSALRHYINLITRQRY to apply alternate derivatives, like the acid form and its amide, to get an agent comprising 2 peptides having the same spectrum of activity as the acid or the amide.

3. Claims 29 to 31, 37-39 are not limited to the second medical use format. They indirectly claim the scope of the originally filed product claim, which is not novel in respect of the neuropeptide Y (RYYSALRHYINLITRQRY) and its known derivatives (D1/D3).

4. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D6 are not mentioned in the description, nor are these documents identified therein.

Claims

1. An isolated nucleic acid molecule which encodes a peptide characterised in that the nucleic acid molecule is selected from the following group:

i) a nucleic acid molecule comprising the nucleic acid sequence presented in figure 6;

ii) a nucleic acid molecule as represented by the sequence presented in figure 6 which has been modified by addition, deletion or substitution of at least one nucleotide base within at least one codon to encode a variant peptide which has cell-cycle inhibitory activity;

iii) a nucleic acid molecule which hybridizes to the sequence in (i) or (ii); and

iv) a nucleic acid molecule comprising a nucleic acid sequence which is degenerate as a result of the genetic code to the sequences identified in (i)-(iii); for the manufacture of a medicament for use in the treatment of diseases or conditions which would benefit from an inhibition of cell-division.

2. A peptide encoded by the nucleic acid according to Claim 1 for the manufacture of a medicament for use in the treatment of diseases or conditions which would benefit from the inhibition of cell division.

3. A peptide according to Claim 2 wherein said peptide inhibits angiogenesis.

4. A peptide according to Claim 2 or 3 wherein said disease is selected from the group consisting of: cancer; psoriasis; neovascular glaucoma; rheumatoid arthritis; diabetic retinopathy.

5. A peptide according to Claim 4 wherein said disease is cancer.

6. A peptide according to Claim 2 or 3 wherein said disease in psoriasis.

7. A peptide according to Claim 6 wherein said psoriatic condition is selected from the group consisting of: nail psoriasis; scalp psoriasis; plaque psoriasis; pustular psoriasis; guttate psoriasis; inverse psoriasis; erythrodermic psoriasis; psoriatic arthritis.

8. A peptide according to any of Claims 2-7 wherein said peptide comprises an amino acid sequence, or part thereof, consisting of the amino acid sequence ARYYSALRHYINLITRQRT.

9. A peptide according to Claim 8 wherein said peptide is a peptide consisting of the amino acid sequence ARYYSALRHYINLITRQRT.

10. A peptide according to any of Claims 2-9 wherein said peptide is a fragment of the peptide ARYYSALRHYINLITRQRT.

11. A peptide according to any of Claims 2-10 wherein said peptide is acetylated.

12. A peptide according to Claim 11 wherein said acetylation is to the amino terminus of said peptide.

13. A peptide according to any of Claims 2-12 wherein said peptide is amidated.

14. A peptide according to Claim 13 wherein said amidation is to the carboxyl-terminus of said peptide.

15. A peptide according to any of Claims 2-10 wherein said peptide, or fragment thereof, is modified by both acetylation and amidation.

16. A peptide according to any of Claims 2-15 wherein said peptide is modified by cyclisation.

17. An agent comprising two or more peptides according to any of Claims 2-16 wherein said agent has cell-cycle inhibitory activity.

18. An agent according to Claim 17 wherein said two or more peptides are linked by a linker molecule.

19. An agent according to Claim 17 or 18 wherein said agent comprises a plurality of peptides.

20. An agent according to Claim 19 wherein said agent comprises 3, 4, 5, 6, 7, 8, 9, or 10 peptides linked together as an oligomeric peptide.

21. An agent according to Claim 17 or 18 wherein said peptide has greater than 10 peptides.

22. An agent according to Claim 17 or 18 wherein said agent is a dimer of two peptides.

23. An agent according to any of Claims 17-22 wherein said linker is a peptide linking molecule.

24. An agent according to Claim 23 wherein said peptide linking molecule comprises at least one amino acid residue which links at least two peptides.

25. An agent according to Claim 23 or 24 wherein said peptide linking molecule comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid residues.

26. An agent according to Claim 23 wherein said linking molecule comprises more than 10 amino acid residues.

27. An agent according to any of Claims 17-26 wherein said agent is a fusion protein comprising an inframe translational fusion.

28. The use of an agent according to any of Claims 17-27 as a pharmaceutical.

29. A pharmaceutical composition comprising an agent according to any of Claims 17-27.

30. A vector comprising a nucleic acid molecule which encodes a peptide and/or agent according to any of Claims 2-27.

31. A cell transformed/transfected with a nucleic acid molecule according to Claim 1 or a vector according to Claim 30.

32. A non-human, transgenic animal characterised in that said animal incorporates a nucleic acid molecule encoding a peptide and/or agent according to any of Claims 2-27.

33. A combined preparation comprising a peptide/agent according to any of Claims 2-27 and at least one cytotoxic agent.

34. A combined preparation comprising a peptide/agent according to any of Claims 2-27 and at least one anti-angiogenic agent.

35. A method to treat an animal which would benefit from inhibition of cell-division comprising:

i) administering an effective amount of an agent comprising a peptide/agent according to any of Claims 2-27, to an animal to be treated;

ii). monitoring the effects of said agent on the inhibition of cell-division.

36. A method according to Claim 35 wherein said treatment is the inhibition of tumour development.

37. A method according to Claim 35 or 36 wherein said agent is a nucleic acid molecule according to Claim 1 or a vector according to Claim 30.

38. An imaging agent comprising a peptide/agent according to any of Claims 2-27.

39. A peptide comprising the amino acid sequence ARYYSALRHYINLITRQRT, or a variant peptide wherein said sequence is modified by addition, deletion of substitution of at least one amino acid residue, for use as a pharmaceutical agent.

40. A pharmaceutical composition comprising a peptide according to Claim 39.